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AGE ASPECTS OF THE COURSE OF CHRONIC OTITIS MEDIA WITH CHOLESTEATOMA IN CHILDREN (CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS)

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Cholesteatoma of the middle ear is the disease, the course and prognosis of which can not be considered without taking into account the patients age. In pediatric otorhinolaryngology, such patients require special attention due to the aggressiveness of cholesteatoma in children. The rapid growth and a high number of recurrences after surgical treatment are features of the course of this disease in children. The causes of the aggressiveness of this disease in children have not been studied. Objective: to identify clinical and immunological features in children with middle ear cholesteatoma in different age groups that contribute to the aggressive course of the disease. A retrospective analysis of 143 medical case reports of children from 1 to 17 years old who received surgical treatment of middle ear cholesteatoma was carried out in the Department of othorhinolaryngology (St. Petersburg State Pediatric Medical University) from 2000 to 2018. Comparative analysis of clinical manifestation, anamnesis of ear disease, concomitant diseases, immunological reactivity (the content of lymphocytes, their subpopulations and interleukin-2 in peripheral blood) and results of surgical treatment of middle ear cholesteatoma in different age groups has been performed. Cholesteatoma is more aggressive in young children. Frequent infections of the upper respiratory tract, eustachian tube dysfunctions, immune disorders in children under 7 years of age lead to an unfavorable course and prognosis of middle ear cholesteatoma.

Keywords: middle ear cholesteatoma in children; congenital cholesteatoma; chronic otitis media; cytokines; immunity.

ВОЗРАСТНЫЕ АСПЕКТЫ ТЕЧЕНИЯ ХРОНИЧЕСКОГО ОТИТА С ХОЛЕСТЕАТОМОЙ У ДЕТЕЙ (КЛИНИЧЕСКАЯ И ИММУНОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА)

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Ярким примером заболевания, течение и прогноз которого невозможно рассматривать без учета возраста больного, является холестеатома среднего уха. В детской оториноларингологии такие пациенты требуют особенно пристального внимания в связи с более агрессивным течением холестеатомы у детей, которое проявляется очень быстрым ее ростом и высоким числом рецидивов после хирургического лечения. Причины агрессивного течения этого заболевания у детей до сих пор остаются предметом изучения. С целью выявить в различных возрастных группах клинические и иммунологические особенности у детей с холестеатомой среднего уха, способствующие агрессивному течению заболевания, проведен ретроспективный анализ историй болезни 143 пациентов от 1 года до 17 лет, оперированных по поводу холестеатомы среднего уха в отделении оториноларингологии СПбГПМУ с 2000 по 2018 г. Оценивались и сравнивались в различных возрастных группах особенности клинической манифестации холестеатомы среднего уха, анамнез заболевания уха, сопутствующая соматическая патология, состояние иммунологической реактивности (содержание лимфоцитов, их субпопуляций и интерлейкина-2 в периферической крови), результаты хирургического лечения. Холестеатома среднего уха имеет тенденцию к более агрессивному течению у детей младшего возраста. Частые инфекции верхних дыхательных путей, тубарные дисфункции, нарушения клеточного и гуморального иммунитета у дошкольников являются фоном, способствующим неблагоприятному течению и прогнозу холестеатомы среднего уха.

Ключевые слова: холестеатома среднего уха у детей; врожденная холестеатома; хронический средний отит; цитокины; иммунитет.

BACKGROUND

Age is the most important factor to determine the characteristics of the manifestation, course, and choice of therapeutic approach and prognosis of many diseases. At each age stage, the child has its own morphological, physiological, and immunological aspects, which, probably, create the prerequisites for a certain course of the disease [6]. Interpretation of the disease clinical presentation from the age perspective of the child allows a differentiated approach to the patient and prediction of the course of the disease, to a certain extent.

A vivid example of a disease, in which the course and prognosis cannot be considered without an age aspect, is cholesteatoma of the middle ear.

Cholesteatoma is a tumor-like formation that consists of a dense mass of epidermis soaked in cholesterol and surrounded by a connective tissue capsule (matrix). There can be congenital and acquired cholesteatoma. Congenital cholesteatoma is considered a malformation of the middle ear as a result of a disorder of branchial fissure formation, whereas acquired cholesteatoma occurs as a result of a long inflammatory process in the middle ear. As the cholesteatoma grows, it destroys the bone structures of both the middle and inner ears, thereby causing life-threatening complications [2].

In pediatric otorhinolaryngology, such patients require especially close attention because of more aggressive courses of cholesteatoma in children, which is manifested by its very rapid growth and a high number of relapses after surgical treatment [11]. However, even in the children's age category, there is a tendency to a more unfavorable course of the disease in young children [3, 4]. A study by Stangerup et al. [10] demonstrated that the percentage of cholesteatoma recurrence in pediatric patients under 8 years old is twice as high as in children over 8 years old (47% and 24%, respectively). The causes of the aggressive course of middle ear cholesteatoma in pediatric patients are still not fully understood.

This study aimed to reveal the clinical and immunological characteristics of pediatric patients with middle ear cholesteatoma in different age groups that contribute to the aggressive course of the disease.

MATERIALS AND METHODS

A retrospective analysis of case histories of 143 patients aged 1 to 17 years (150 cases, since seven patients had cholesteatoma on both sides), who were operated for middle ear cholesteatoma in the ear, nose, and throat (ENT) department of the St. Petersburg State Pediatric Medical University from 2000 to 2018, was performed. Complete clinical, laboratory, bacteriological, radiological, audiometric, and detailed immunological examinations were conducted to the patients. Within this study, the pediatric patients were divided into groups according to the age periodization proposed by Russian pediatrician Gundobin, namely, toddlers (1–3 years), preschoolers (3–7 years), primary school-aged children (7–11 years old), and secondary school-aged children (12–18 years) [1]. Then, the positions were evaluated and compared in age groups, namely, the clinical manifestation of middle ear cholesteatoma, anamnesis of ear disease, concomitant somatic pathology, immunological reactivity state, surgical treatment results, and percentage of cholesteatoma relapse.

The state of cellular immunity (the lymphocytes count and their subpopulations in the peripheral blood) was assessed, and the content of interleukin-2 (IL-2) in the blood serum and its production by peripheral blood mononuclear cells (PBMC) was determined.

The level of IL-2 in blood serum and supernatants of blood samples was determined using commercial test systems developed at the National Research Institute for High Purity Biologicals (St. Petersburg). These test systems are based on the "sandwich" method of enzyme-linked immunosorbent assay using horseradish peroxidase as an indicator enzyme. The level of IL-2 in the supernatants of blood samples cultured without inducers was evaluated as spontaneous production of cytokines by peripheral blood cells, and in the presence of an inducer, it was evaluated as induced production of PBMC cytokines. Phytohemagglutinin at a final concentration of 50 μg/mL was used to stimulate the production of IL-2.

Lymphocyte subpopulations CD3+ (T-lymphocytes), CD4+ (T-helper cells), CD8+ (T-cytotoxic lymphocytes), CD20+ (B-lymphocytes), CD16+ (natural killer cells), and CD25+ (IL-2 receptors) were identified using monoclonal antibodies made by Medbiospectr (Moscow). Fresh heparinized blood was diluted two times with physiological saline and layered on a separation medium (Ficollverographene gradient with a density of 1.077 g/cm^3) in a centrifuge tube in a ratio of 2.5:1, after which it was centrifuged for 30 min at an acceleration of 400 g. After centrifugation, the resulting mononuclear ring was pipetted, and the resulting cell suspension was washed three times with physiological saline and adjusted to a concentration of 2×10^6 cells/mL. For the quantitative determination of peripheral blood lymphocyte subpopulations, the standard method of a two-stage complement-dependent lymphocytotoxic test was used. Suspension of lymphocytes (1 μL) was added to the wells and incubated for 40 min at 20 °C, and then, 5 μL of rabbit complement was added to each well (Russian Research Institute of

Hematology and Transfusiology, St. Petersburg). After this, incubation was performed for 60 min at 20 °C. To stain cells, 2 μL of a 5% aqueous eosin solution was added to each well, and after 2 min, 5 μL of a 17% formalin solution was fixed. The results were evaluated using a light microscope at 150-fold magnification. The number of stained (specifically reacted) lymphocytes was calculated for each subpopulation in three parallels, at least 100 cells in each. The mean value, expressed as a percentage of the number of counted cells, was determined. The absolute number of cells in 1 mm^3 was calculated using data from a clinical blood test performed on the same day (white blood cell count and relative lymphocyte count).

The data of a study by Ketlinsky et al. [5] were taken as normal age indicators of the content of various lymphocyte subpopulations in the peripheral blood. As a control group, immunological parameters of pediatric patients aged 4.5 to 16 years ($n = 23$), who were examined at the Children's Hospital No. 2 with the diagnoses of cardiac functional murmur and vegetovascular dystonia and who did not have acute infectious disease manifestations, chronic pathology exacerbations, and ear disease signs at the time of examination and during the previous month, were used.

Blood samples were taken for immunological studies before the start of systemic and topical antibacterial and anti-inflammatory therapy. Immunological studies were conducted in the immunopharmacology laboratory of the National Research Institute for High Purity Biologicals. Statistical data processing was performed using Excel software of Microsoft Office 2000. The differences between the two average values were evaluated according to the Student's test. The difference between the compared indices was considered significant at $p < 0.05$.

RESULTS

Toddler Group (1–3 Years Old) – Seven Patients (Eight Cases)

The clinical disease manifestation of this age group is characterized by an acute onset in the form of earache, fever, and intoxication. In a hospital or clinic, acute otitis media was diagnosed in the patients; the standard treatment was prescribed; paracentesis was performed in two patients, but pus was not taken. The lack of normalization of the otoscopic presentation necessitated computed tomography of the temporal bones, which revealed bone-destructive changes. The period from the onset of the disease to surgery was 2.3 ± 1.4 months. In all eight cases during the surgery, a common creeping cholesteatoma was found, which was regarded as congenital in the absence of any history of ear disease. Relapse of the disease was registered in all patients (100%) of this age group 6–12 months after surgery, because of this, the pediatric patients underwent repeat surgery represented by radical general cavity surgery.

Preschool Group (3–7 Years Old) – 29 Patients (31 Cases)

In 11 cases (35%), cholesteatoma was regarded as congenital. The clinical disease manifestation in pediatric patients of this age group did not differ from the manifestation in pediatric patients under 3 years of age. Creeping cholesteatoma spreading over the cavities of the middle ear is typical, which requires a large amount of surgery.

Nineteen preschoolers (65%) were included in the group of frequently and chronically ill children (seven or more episodes per year or 10 acute respiratory diseases over the past 2 years [7, 9]). The high incidence of respiratory viral and bacterial infections and characteristics of pediatric patients of this age contributed to the infection of the middle ear. Of pediatric patients, 79% had a history of at least one episode of otitis media (23 patients). In 10 patients, otitis media had a relapsing course (three or more episodes for 6 months or four episodes per year). The period from the disease manifestation to surgery was 8.6 ± 6.3 months.

Because the process of maturation of the child's immune system passes through several age stages, and certain specific aspects of the immune status correspond to each age, it was interesting to study the number of lymphocytes and their subpopulations in peripheral blood in patients with middle ear cholesteatoma [8].

In the group of patients aged 4 to 7 years with a cholesteatoma-destructive process, there was a tendency to decrease in all lymphocyte subpopulations compared with the age norm; significant differences were obtained when assessing the absolute count of CD3 ($p < 0.01$) and CD4 ($p < 0.001$) and the relative count of CD8 and B-lymphocytes ($p < 0.05$). When comparing with the control group, a significant decrease in the absolute and relative number of CD25 ($p < 0.01$) was revealed, as well as an increase in the relative count of B-lymphocytes (Table).

Given the changes identified in the T-system of immunity, a study of IL-2, which is the main growth factor of T-lymphocytes, was conducted. Spontaneous production of PBMC IL-2 was equal to zero, which corresponded to the norm. The average value of the induced production of IL-2 by PBMC in pediatric patients aged 4–7 years was 1.1 ± 1.0 units/mL, whereas the value in the control group was 11.1 ± 0.44 units/mL.

Table / Таблица

The content of lymphocytes and their subpopulations in the peripheral blood of patients with middle ear cholesteatoma in different age groups, children of the control group and normal

Содержание лимфоцитов и их субпопуляций в периферической крови у больных с холестеатомой среднего уха в разных возрастных группах, детей контрольной группы и в норме

Lymphocytes / Лимфоциты	Age categories / Возрастные группы				Control group 4–15 years (*n* = 32) / Контрольная группа 4–15 лет (*n* = 23)
	4–6 years (*n* = 11) / 4–6 лет (*n* = 11)	Norm / Норма	7–17 years (*n* = 32) / 7–17 лет (*n* = 32)	Norm / Норма	
Lymph., % / Лимф., отн., %	42.7 ± 12.8 (32–67)	46 (38–53)	43.4 ± 12.0 (21–66)	40 (36–43)	–
Lymph., abs/μl / Лимф., абс. тыс./мкл	2.7 ± 1.3 (1.6–5.4)	3.6 (2.9–5.1)	2.4 ± 0.7 (1.1–3.8)	2.4 (2–2.7)	–
CD3, % / CD3, отн., %	63.3 ± 10.8 (46–74)	64 (62–69)	57.3 ± 12.0* (35–80)	70 (66–76)	57.6 ± 1.7 (48–66)
CD3, abs/μl / CD3, абс. тыс./мкл	1.6 ± 0.4* (1.2–2.5)	2.5 (1.8–3)	1.4 ± 0.5*.** (0.5–2.5)	1.8 (1.4–2)	1.6 (1–1.8)
CD4, % / CD4, отн., %	32.3 ± 8.7 (16–45)	37 (30–40)	32.1 ± 9.6* (12–51)	37 (33–41)	30.7 ± 1.5 (20–42)
CD4, abs/μl / CD4, абс. тыс./мкл	0.8 ± 0.1* (0.6–1.0)	1.6 (1–1.8)	0.8 ± 0.3 (0.3–1.7)	0.8 (0.7–1.1)	0.8 ± 0.2 (0.3–1.8)
CD8, % / CD8, отн., %	25.7 ± 3.4* (21–30)	29 (25–32)	22.5 ± 5.2* (13–34)	30 (27–35)	24.1 ± 1.5 (14–36.5)
CD8, abs/μl / CD8, абс. тыс./мкл	0.7 ± 0.3 (0.4–1.4)	0.9 (0.8–1.5)	0.6 ± 0.2* (0.2–1.2)	0.8 (0.6–0.9)	0.6 ± 0.07 (0.2–1.0)
CD4/CD8 / CD4/CD8	1 ± 0.4 (0.6–1.9)	1.3 (1.0–1.6)	1.5 ± 0.7 (0.6–3.9)	1.3 (1.0–1.4)	1.3 ± 0.07 (0.9–1.9)
B-Cells, % / B-Лимф., отн., %	19.7 ± 6.2*. ** (12–29)	24 (21–28)	16.1 ± 6.6** (5–30)	16 (12–22)	12.9 ± 0.8 (8.5–18.3)
B-Cells, abs/μl / B-Лимф., абс. тыс./мкл	0.6 ± 0.5 (0.3–1.6)	0.9 (0.7–1.3)	0.4 ± 0.2 (0.2–1.0)	0.4 (0.3–0.5)	0.3 ± 0.04 (0.1–0.5)
CD16, % / CD16, отн., %	10.5 ± 5.4 (5–20)	(8–15)	16 ± 8.9 (5–44)	(9–16)	13.1 ± 1.1 (9–22)
CD16, abs/μl / CD16, абс. тыс./мкл	0.3 ± 0.3 (0.1–0.8)	0.4 (0.2–0.6)	0.4 ± 0.3 (0.1–1.5)	0.3 (0.2–0.3)	0.4 ± 0.06 (0.1–0.7)
CD25, % / CD25, отн., %	5.4 ± 5.0** (1.1–14)	(8–12)	7.2 ± 8.6** (0.6–36)	(10–16)	16.7 ± 1.1 (11–26)
CD25, abs/μl / CD25, абс. тыс./мкл	0.1 ± 0.1** (0.03–0.3)	(0.3–0.48)	0.2 ± 0.17** (0.02–0.9)	(0.2–0.36)	0.4 ± 0.1 (0.2–0.8)

Note. *Significance of differences when comparing groups of children with cholesteatoma and content of the age norm. **Significance of differences when comparing groups of children with cholesteatoma and control groups. The range (minimum–maximum) is indicated in parentheses.

Примечание. *Достоверность различий между группами больных и показателями возрастной нормы. **Между группами больных и контролем. В скобках указан диапазон (минимум–максимум).

The diseases were identified in the structure of concomitant pathology in pediatric patients of this age group, namely, cerebral palsy in one patient and delayed psychoverbal development in one person.

The relapse of cholesteatoma during hearing-sparing surgeries was 58% with a follow-up period of 6 to 12 months.

Primary School-Aged Group (7–11 Years Old) – 52 Patients (55 Cases)

The proportion of patients with congenital cholesteatoma in the primary school-aged children is significantly lower than that in the younger age groups (11%, six cases). The clinical presentation of the congenital cholesteatoma manifestation has also changed, which

included unilateral conductive hearing loss and epidermal masses behind the tympanic membrane. The number of frequently and chronically ill children in this age group decreased to 20% (10 patients). The period from the disease manifestation to the surgery was 28.9 ± 25 months. Typically, 89% of the pediatric patients had a history of ear diseases, namely, otitis media episodes (15 patients), recurrent otitis media (15 patients), chronic otitis media diagnosis with a defect in the tympanic membrane (16 patients), repeated otoblennorrhea hospital treatment (26 patients), ear polypectomy (5 patients), and tympanic cavity shunting (2 patients). A history of adenoidectomy was revealed in 30 patients (58%).

Immunological examination revealed a significant decrease in comparison with the norm of the absolute and relative counts of CD3 and CD8 ($p < 0.001$), as well as relative CD4 ($p < 0.01$). The total count of lymphocytes and CD16, as well as the content of B-lymphocytes in the peripheral blood, corresponded to the age norm. When comparing with the control group, a significant decrease in the absolute and relative number of CD25 ($p < 0.001$) and an increase in the relative count of B-lymphocytes were revealed, as well as a decrease in the absolute count of CD3 ($p < 0.05$; Table).

Induced production of IL-2 by PBMC is reduced, but it is twice as high as in the preschool group (2.3 and 1.2 units/mL).

The following diseases were revealed in the structure of concomitant somatic pathology in pediatric patients of this age group: heart defects in five patients, obesity in five, juvenile arthritis in one, kyphoscoliosis in one, cerebral palsy in two, bronchial asthma in six, and tuberculosis in two. The relapse of cholesteatoma during hearing-sparing surgeries was 53% with a follow-up period of 6 to 12 months.

Secondary School-Aged Group (12–18 Years Old) – 55 Patients (56 Cases)

In this age group, congenital cholesteatoma was diagnosed in only three cases (5.4%). Clinical manifestations of the disease included unilateral conductive hearing loss and epidermal masses behind the tympanic membrane.

For secondary school students, as well as for pediatric patients of primary school age, a rather long period from the disease manifestation to surgery is typical, 28 ± 20.7 months (2 months to 8 years). Thus, in 30 pediatric patients, the duration of chronic otitis media with a tympanic membrane defect exceeded 2 years. During this period, patients repeatedly received conservative treatment in an ENT hospital, as well as ear polypectomy, transtympanic bypass surgery, and antibacterial therapy.

An immunological examination revealed a decrease in comparison with the norm of the absolute and relative amounts of CD3 and CD8, as well as relative CD4. Twelve patients (21%) had somatic pathology: two had heart defects, three had kidney malformations or pyelonephritis, one had ulcerative colitis, one had cerebral palsy, two had obesity, one had Down syndrome, and two had tuberculosis. The relapse of cholesteatoma during hearing-sparing surgeries in this age group occurred in 16 cases and amounted to 29% with a follow-up period of 6 to 12 months.

CONCLUSIONS

Middle ear cholesteatoma tends to have a more unfavorable course in young pediatric patients, which is expressed in a higher percentage of disease recurrence after surgery. In the toddler group, cholesteatoma recurrence occurred in 100% of cases, and it was 58%, 53%, and 29% in the preschool, primary school-aged, and secondary school-aged groups, respectively.

Pediatric patients of younger age groups are typically diagnosed with a high rate of congenital cholesteatoma. Congenital cholesteatoma was diagnosed in 100% of cases in the toddler group, 35% in the preschool group, 11% in the primary school-aged group, and 5.4% in the secondary school-aged group. Moreover, depending on age, the clinical presentation of the manifestation also changes; thus, acute inflammatory onset in pediatric patients under 7 years of age and unilateral conductive hearing loss in school-aged pediatric patients are registered.

Chronic otitis media with cholesteatoma in pediatric patients proceeds along with disorders of the T-cell system of immunity and systemic production of PBMC IL-2, with more pronounced immunological disorders registered in preschool patients. According to the literature, impaired production of T-cell growth factor IL-2 in combination with a decrease in the number of cells having mature T-lymphocyte markers indicates the formation of secondary immunodeficiency [9].

Frequent upper respiratory tract infections, tubal dysfunctions, and cellular and humoral immunity disorders in preschool pediatric patients constitute the background contributing to a more unfavorable course and prognosis of cholesteatoma of the middle ear.

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